

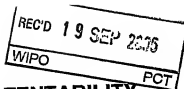
PATENT COOPERATION TREATY


PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference KB528PCT/DGB		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCTGB2004/004464		International filing date (day/month/year) 21.10.2004	Priority date (day/month/year) 21.10.2003	
International Patent Classification (IPC) or national classification and IPC C07C205/11, C07C255/50, C07C323/25, C07D213/74, A61K31/04, A61K31/435, A61K31/277, A61K31/10, A61P5/28				
Applicant KARO BIO AB et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p style="margin-left: 20px;"><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 20px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the International application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 20.06.2005		Date of completion of this report 16.09.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523658 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Goetz, G Telephone No. +49 89 2399-		



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-67

as originally filed

Claims, Numbers

1-31

as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-17
	No: Claims	18-31
Inventive step (IS)	Yes: Claims	
	No: Claims	1-31
Industrial applicability (IA)	Yes: Claims	1-31
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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- D1: WO 01/58854 A (BIOPHYSICA, INC) 16 August 2001 (2001-08-16)
D2: WO 02/16310 A (GTX, INC; DALTON, JAMES; MILLER, DUANE, D; YIN, DONGHUA; HE, YALI) 28 February 2002 (2002-02-28)
D3: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KELLER, HELMUT ET AL: "Oxidative hair dye composition comprising a 2,5-diaminobenzonitrile" XP002320584 retrieved from STN Database accession no. 127:311348
D4: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HASHIZUME, KAZUNARI ET AL: "Oxidizable color-producing reagents containing p-fluoroaniline derivatives" XP002320585 retrieved from STN Database accession no. 117:127839
D5: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TEACH, EUGENE G.: "Herbicidal oxazolidines and methods of use" XP002320586 retrieved from STN Database accession no. 108:217796
D6: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SUDA, HIDEAKI ET AL: "p-Nitroaniline derivatives" XP002320587 retrieved from STN Database accession no. 81:25336
D7: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ZORINA, L. N. ET AL: "New approach to the synthesis of N-aryl-1,3-oxazolidines and N-aryl-1,3-tetrahydrooxazines" XP002320588 retrieved from STN Database accession no. 112:216820

1. The compounds disclosed in D3 to D7 (see the RNs cited in the international search report) fall within the scope of present claims 18 to 31.
The subject matter of present claims 18 to 31 is thus not novel over the prior art disclosed in D3 to D7 (PCT Article 33.2).
2. D1 as well as D2 can be regarded as the closest prior art documents.
Both documents disclose compounds which are active as modulator of the androgen receptor and are due to this activity useful in the treatment of diseases caused by disturbance in the activity of the androgen receptor.
The compounds of D1/D2 differ from the compounds according to general formula I

of present claims 1 and 18 by the fact that the prior art compounds show an amide structure which is not within the claimed scope: see the definition of R_1 and R_2 (R_1 and R_2 cannot form a ketogroup together).

Novelty of the subject matter of present claims 1 to 17 is thus given over the disclosure of D1 as well as D2 (PCT Article 33.2).

3. In view of D1 / D2 the underlying problem can be defined by the provision of further compounds which show the same pharmacological activity, namely modulation of the androgen receptor.
- To represent a solution all compounds falling within the scope of formula I should be active as modulators of the androgen receptor. This has to be shown by a representative number of examples covering the whole scope all possible structures of the claimed general formula.

In the present case only a limited amount of examples is given: see the results of the 14 examples given in the table of page 67.

The structure of the compounds tested is restricted to compounds according to general formula I where

R_5 represents nitro or cyano

X represents NH

Y represents hydroxy or $\text{NH}(\text{C}_1\text{-C}_{10}\text{heteroaryl})$

Such a restricted amount of examples where the general formula is very specified by restriction of the substituents to specific definitions is not considered to be the basis for a generalisation. In particular in the field of receptor-pharmacology it is a well-known and well-recognized fact that even small changes in the structure of a biologically active compound may lead to dramatic changes in the activity. This is supported by the fact that the compounds disclosed in D3 to D7 although falling within the scope of the general formula show quite different activities such as use in hair dying compositions, use in the preparation of herbicides etc.

Consequently a solution of the underlying problem is only acknowledged for those compounds which have been tested since it is evident for the skilled person that these tested compounds cannot be regarded as being representative for all

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compounds falling within the scope of general formula I.

In the absence of a solution over the whole scope an inventive step is missing for present claims 1 to 31 (PCT Article 33.3).

4. Industrial applicability is given for all claims 1 to 31 (PCT Article 33.4).
5. The prior art as disclosed in D1 to D2 is not mentioned in the description.